

# Immunotherapy and Tolerance—Cutting Edge

In *Allergology International* (AI) Vol. 62 No. 4, we offer a series of review articles entitled “Immunotherapy and Tolerance - Cutting Edge”, original articles, and letters to the editor. We believe that this issue of the journal will be of great help for both clinical and basic investigators working in this field.

Conventional subcutaneous injection has been the standard practice in allergen immunotherapy since it was first described by Dr. Noon more than 100 years ago.<sup>1</sup> Its efficacy and safety have been demonstrated by a number of clinical studies, including the first double-blind controlled trial reported by Dr. Frankland.<sup>2</sup> Dr. Durham has reevaluated the clinical and mechanical significance of immunotherapy in recent years from a novel point of view and has made important contributions to this field.<sup>3-6</sup> To introduce this review series, Dr. Durham's group briefly reviews the current understanding of the efficacy and mechanisms of immunotherapy.<sup>7</sup>

Although conventional subcutaneous injection of allergen extracts is still the mainstay of treatment, sublingual immunotherapy is now recognized as an as effective and safe alternative, especially in Europe. Sublingual tablets are now close to market in both the USA and Japan. Dr. Canonica has been influential in the introduction of sublingual immunotherapy into the clinic.<sup>8-11</sup> Here, Dr. Canonica's group comprehensively reviews the emerging role of sublingual immunotherapy and discusses future directions for this approach.<sup>12</sup>

Because immunotherapy is found worldwide in allergy clinics, the underlying mechanisms involved in its use have been studied extensively. Dr. Akdis's laboratory, a pioneering group, studied the role of tolerance in subcutaneous immunotherapy against bee venom among beekeepers.<sup>13,14</sup> For this issue, Dr. Akdis's group presents an extensive review of the studies conducted on the mechanisms of immunotherapy and induction of tolerance, with a discussion of potential directions for immunotherapy in the future.<sup>15</sup>

Among the eight original articles and three letters-to-the-editor in this issue, Yokooji *et al.* report the identification of the allergens in hydrolyzed wheat proteins (HWP)-dependent exercise-induced anaphylaxis (WDEIA).<sup>16</sup> HWP-WDEIA, used in a popular brand of facial soap, has recently become a big social

problem in Japan. Many Japanese patients with HWP-WDEIA have the unique characteristic that they develop allergic reactions following exercise after ingesting natural wheat products. This contrasts with HWP-WDEIA in European patients suffering from immediate allergic reactions when they eat HWP-containing food, while they can eat normal wheat products without problems. The authors speculate that a specific-IgE to HWP cross-reacting with wheat proteins exists in Japanese HWP-WDEIA patients, finding that IgE antibodies recognizing  $\alpha/\beta$ -,  $\gamma$ - and  $\omega$ 1,2-gliadin, components of gluten, are causative allergens in these patients. This is useful information for diagnosis and desensitization therapy for HWP-WDEIA. Ashok Kumar *et al.* report gene cloning of an allergen from sapodilla whose fruits occasionally cause oral allergy syndrome. The identified new allergen, an acidic thaumatin-like protein (TLP), is homologous with other known allergic TLPs contained in olives, grapes, kiwis, bell peppers, and tobacco.<sup>17</sup>

We appreciate all the authors for their contributions to the present issue of *Allergology International*.

Akio Mori  
Associate Editor, *Allergology International*

Kenji Izuhara  
Editor-in-Chief, *Allergology International*

## REFERENCES

1. Noon L. Prophylactic inoculation against hay fever. *Lancet* 1911;1:1572.
2. Frankland AW, Augustin R. Prophylaxis of summer hay fever and asthma: controlled trial comparing crude grass pollen extracts with isolated main protein component. *Lancet* 1954;1:1055.
3. Varney VA, Hamid QA, Gaga M *et al.* Influence of grass pollen immunotherapy on cellular infiltration and cytokine mRNA expression during allergen-induced late-phase cutaneous responses. *J Clin Invest* 1993;92:644-51.
4. Durham SR, Ying S, Varney VA *et al.* Grass pollen immunotherapy inhibits allergen-induced infiltration of CD4+ T lymphocytes and eosinophils in the nasal mucosa and increases the number of cells expressing messenger RNA for interferon-gamma. *J Allergy Clin Immunol* 1996;97:1356-65.
5. Durham SR, Walker SM, Varga EM *et al.* Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med*

- 1999;**341**:468-75.
6. James LK, Shamji MH, Walker SM *et al*. Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies. *J Allergy Clin Immunol* 2011;**127**:509-16.e1-5.
  7. Matsuoka T, Shamji MH, Durham SR. Allergen Immunotherapy and Tolerance. *Allergol Int* 2013;**62**:403-13.
  8. La Rosa M, Ranno C, André C, Carat F, Tosca MA, Canonica GW. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized *Parietaria judaica* extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999;**104** (Pt 1): 425-32.
  9. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Clinical, functional, and immunologic effects of sublingual immunotherapy in birch pollinosis: a 3-year randomized controlled study. *J Allergy Clin Immunol* 2005;**115**:1184-8.
  10. Canonica GW, Bousquet J, Casale T *et al*. Sub-lingual immunotherapy: World Allergy Organization Position Paper 2009. *Allergy* 2009;**64**(Suppl 91):1-59.
  11. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. *J Allergy Clin Immunol* 2010;**126**:969-75.
  12. Compalati E, Braidò F, Canonica GW. Sublingual Immunotherapy: Recent Advances. *Allergol Int* 2013;**62**:415-23.
  13. Akdis CA, Akdis M, Blesken T *et al*. Epitope specific T cell tolerance to phospholipase A2 in bee venom immunotherapy and recovery by IL-2 and IL-15 in vitro. *J Clin Invest* 1996;**98**:1676-83.
  14. Akdis CA, Blesken T, Akdis M, Wuthrich B, Blaser K. Role of interleukin 10 in specific immunotherapy. *J Clin Invest* 1998;**102**:98-106.
  15. Jutel M, van de Veen W, Agache I, Azkur KA, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy and novel ways for vaccine development. *Allergol Int* 2013;**62**:425-33.
  16. Yokooji T, Kurihara S, Murakami T *et al*. Characterization of causative allergens for wheat-dependent exercise-induced anaphylaxis sensitized with hydrolyzed wheat proteins in facial soap. *Allergol Int* 2013;**62**:435-45.
  17. Ashok Kumar HG, Hegde VL, Shetty SM, Venkatesh YP. Characterization and gene cloning of an acidic thaumatin-like protein (TLP 1), an allergen from sapodilla fruit (*Manilkara zapota*). *Allergol Int* 2013;**62**:447-62.